THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1916

ORIGINAL ARTICLES

THE DIAGNOSIS AND GENERAL TREATMENT OF SYPHILIS.

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(Read before the Congress of American Physicians and Surgeons, Washington, D. C., May 9 and 10, 1916.)

It cannot be emphasized too frequently nor too emphatically that the fate of the syphilitic individual depends largely upon the early diagnosis of his infection and the intensity with which his treatment is carried out in the first six months. It is in the accomplishment of this purpose that the modern aids to diagnosis have rendered such invaluable service. Unfortunately, this is not universally recognized, for clinicians are still met with who decry these modern precision methods, claiming that the trained observer can recognize with his eye and sense of touch all that can be revealed by laboratory procedures. The fallacy of this claim is demonstrated from time to time by patients who come with the following history: Fifteen to twenty years ago they consulted the best-known syphilographer at that time, who made a diagnosis of chancroid, telling the patient that his future, as far as the present infection was concerned, was secure and that he had nothing to fear. Reassured by such information no treatment was taken, and years after these patients consult for involvement of the central nervous system, an interstitial glossitis, an aortitis, or other late manifestation of the disease. It is now well known that the soft sore frequently harbors the parasite of syphilis, and owing to the longer incubation period of the latter, does not develop its characteristic features until after the expiration of two or three weeks, or they may be entirely absent. It seems superfluous, therefore, to insist that the secretion of all venereal sores be searched for the Treponema pallidum. Failing to find it, one should not give a favorable prognosis until repeated examinations have been made, including the Wassermann reaction. With proper training the dark-field illumination is simple of application and the spirochete of syphilis readily differentiated from other types. Microscopic corroboration of a suggestive sore is absolutely essential in many cases, owing to the protean appearance chancres may assume. While, to the skilled eye and finger, a Hunterian chancre with indurated edges needs no confirmation, the pathognomonic features may be lacking altogether, or a papule or herpetic lesion may represent the only local reaction called forth by the treponema. In urethral sores and suspicious extragenital lesions the correct and early diagnosis is of great importance, and their nature finds a ready means of differentiation in the dark field. The value of the latter is further appreciated in developing chancres before the clinical characteristics suggestive of the infection appear. Recently, I had the opportunity to examine an initial lesion which had made its appearance only on that day. It was situated on the left side of the foreskin, was about the size of a pinhead, capped by a tiny crust. The patient had been exposed three weeks before. There was no lymph-node enlargement and the Wassermann reaction was negative. The advantage of early treatment in such cases and consequently the more favorable prognosis are too obvious for discussion. Success in demonstrating the organism depends largely on the care taken in obtaining serum for examination. This should be secured from the depths of the lesion. Antiseptic washes, ointments, or other applications frequently interfere with the demonstration, and in cases of doubt the examination should be repeated on successive days, the lesion being kept clean meanwhile with saline solution.

The time of the appearance of the Wassermann reaction cannot be estimated with mathematical exactness, as it is dependent upon the rapidity with which the organisms gain the general circulation and the reaction provoked by them. This we know varies in different individuals. In some cases the reaction is positive in the fourth or fifth week after exposure; in others not until the seventh or eighth week. A negative reaction does not necessarily mean that generalization of the spirochetes has not taken place. Uhlenhuth and Mulzer[1] obtained positive results in animal inoculations with the blood of primary syphilitics in whom the Wassermann reaction was still negative. With the development of the rash it is usually definitely established. I have in a very long series of untreated cases found only one with a fresh maculopapular eruption in which the Wassermann was only weakly positive. If treatment is carried out on a definite and intensive plan in the primary stage a negative reaction will remain continuously negative, or in the event of its being already positive it shows itself susceptible of reversion more readily than when the infection is of several years' duration. Too much stress cannot be laid on the fact that the amount of treatment is individual; this must be kept in view in every case under consideration. There are patients treated under the old régime with mercury by mouth, inunctions or injections, or these methods combined, who now have a negative blood reaction, exhibit no symptoms referable to the nervous or circulatory system, and are negative after a provocative injection of salvarsan. Others treated five years ago with a minimum amount of salvarsan (*i. e.*, one or two injections) and mercury may likewise be considered cured according to our present-day criteria. On the other hand, there are a certain number of patients in whom multiple courses of salvarsan and mercury are necessary to bring about and maintain negative findings. In some cases we will even fail to convert a positive into a negative reaction without endangering the health of the patient. A resistant serum cannot always be accounted for on a clinical basis, for often, as far as we are able to ascertain, nothing can be demonstrated to explain its persistence. In by far the vast majority, however, involvement of the cardiovascular or nervous system will furnish an explanation.

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[1] Berl. klin. Wchnschr., 1913, p. 769.

The interpretation of the Wassermann reaction is as important as that of the clinical phenomena of the disease, but the burden of proof should not rest with its presence or absence alone. In ocular syphilis, disease of the vascular apparatus, obscure visceral or nervous involvement and in latent syphilis of hereditary origin positive manifestations may be present and the Wassermann reaction negative. To make some of these points clear the following cases are quoted:

CASE I.—Man, with active secondary skin and throat lesions at end of October, 1914. On October 31, November 8 and 20, and December 13 respectively, 0.6 gm. salvarsan. January 8, 1915, perivasculitis. Wassermann said to have been negative. Under rubbings and calomel, eye lesions cleared. Discontinuance of treatment was followed by relapse from a new focus. March 31: Spinal fluid, ——; serum, ——. Under injections of a soluble salt and potassium iodide the eyesight again improved. Treatment interrupted in September. Wassermann, December 29, 1915, March 16, 1916, + + + +.

CASE II.—Man, aged fifty-seven years, with cerebral endarteritis and capillary fibrosis at the maculæ. Infection over thirty years ago. Recurring ulcerative skin lesions; scaling eruption palms; mental depression, vertigo, loss of memory; inability to concentrate on work;

failure of sexual power. He recalls severe headaches, leg pains, and mental excitability in secondary period twenty-nine years ago. Eye reflexes, knee-jerks, and ankle-jerks present without noticeable abnormality. Treatment during many years with mercury and potassium iodide. Repeated negative Wassermann reactions during 1911 and 1912. In 1913, after treatment with potassium iodide and mercury, Wassermann became + + + +, and after further treatment ——. Spinal fluid March 31, 1915: cells, 0; globulin, + +; Wassermann, ——; gold test, ——; blood Wassermann, + + + +. Treatment continued during 1915 was followed by improvement in all respects. Vertigo and depression disappeared; capacity for work increased. He was less excitable and memory and sexual power returned. Evidence of vascular disease in eye also disappeared.

The noteworthy features in this case are the long persistence of a negative Wassermann reaction, with scaling palms analogous to leukoplakia, the obscure character of the nervous symptoms, evidence of vascular disease in eyes, result of fluid examination pointing to cerebral endarteritis, Wassermann reaction becoming positive after treatment by iodides and mercury, and relief of all symptoms by persistent treatment.

CASE III.—Girl, aged twenty-one years; hereditary syphilis. Scars of an old interstitial keratitis. For five years had suffered from migraine type of headache. Serum ——; spinal fluid ——. After three injections of salvarsan serum became strongly positive.

CASE IV.—Man, aged forty-nine years; chancre when sixteen years old, followed by secondaries. For three years internal treatment; no relapses. In the summer of 1915 he complained of increasing fatigue and soreness over the right apex. Repeated examinations for tubercle bacilli negative. Von Pirquet, +; Wassermann, ——. From roentgen-ray and physical examination, diagnosis of syphilis of the bronchial glands was made. Wassermann, January 7, 1916, ——; January 11, 1916, ——; mixed treatment for one week evoked a + + + + reaction.

The above abstracts show that not rarely it requires not a single but several injections of salvarsan or the prolonged use of mercury and potassium iodide before a provocative reaction is obtained.

The Wassermann test is of great value in the recognition of syphilis as a causative factor in conditions of obscure etiology in children. Also in anticipating future development, as in many cases of congenital syphilis no sign or symptom is present excepting a positive blood reaction. The children are normal mentally and physically, and excepting the positive serum and a history of syphilis in the father there is nothing suggestive of a luetic taint.

The tendency of the present day is to deny categorically the paternal origin of syphilis, admitting only the possibility of transmission from the maternal side. While this would simplify the problem it offers no solution for the cases in which the mothers remain symptom-free and Wassermann-negative; some patients observed after thirty years who have had one or more children clinically and serologically syphilitic. Do such women have a modified form which disappears spontaneously or do they escape the infection altogether?

The only criterion of cure in a man contemplating matrimony is a negative Wassermann which has persisted for at least a year after intensive treatment and which remains negative after a provocative salvarsan. The element of time while of importance in modifying the infection is of vastly less value than the revelation of the serological test. In a family seen by me a short time ago the father was infected in 1901, for which he had inunctions and potassium iodide each year for six years. He was married in 1907. The first child was born in 1908, was well nourished and healthy until August, 1915, when he developed partial deafness of the right ear. His spinal fluid showed: cells, 20; globulin, + +; Wassermann, ——; serum, + + +. The second child was born in 1913, is splendidly developed in every way, and has never shown any symptoms but has a + + + + Wassermann. The mother's reaction is negative; she has never given any evidence of the infection, has had no miscarriages and no treatment. The father's reaction is + + + +.

The diagnostic import of the spinal-fluid examination grows more and more apparent with time. The cell count, Wassermann reaction, globulin and colloidal gold tests enable us not only to determine the activity of a syphilitic process in the brain or cord but serve to distinguish the various pathological types of syphilis affecting the cerebrospinal system and in many cases to differentiate between these and non-luetic affections. A case in point is the simulation of the multiple neuritis of diabetes by the tabetic syndrome.

A patient, aged thirty-seven years, was referred to me with the diagnosis of tabes. He had had a chancre twelve years before, followed by secondaries and treatment for three years. For four weeks he had had pain and numbness in his fingers and feet, with an insecure feeling in the soles of his feet, difficulty in walking and unsteadiness. For six or seven years he had had periodic attacks of gastric distress, with dizziness and extensive areas of hyperesthesia; sexual paresis had been present for one year; eyes were normal; patella and Achilles reflexes absent. Laboratory examination showed: blood Wassermann, ——; spinal fluid; cells, 8; globulin, ——; Wassermann, ——. His urine contained a large amount of sugar. Diagnosis: diabetic polyneuritis.

Another case was sent with the diagnosis of taboparesis. The patient gave a history of syphilis twenty-five years previously, with repeated courses of treatment. His pupils were irregular and fixed to light, knee-jerks absent and lightning pains in the lower extremities. It was claimed that he had shown evidence of mental deterioration as manifested by irascibility, loss of memory, etc. The patient had been an alcoholic for over thirty years, having taken six to eight drinks daily, with occasional intermissions. His blood and fluid examinations were absolutely negative. In this case a correct diagnosis might have been made by a skilled diagnostician, but to the average practitioner the picture presented was that of tabes or taboparesis. From the laboratory stand-point there are two possible conclusions: either the spinal-fluid findings were rendered negative by the treatment received or the entire syndrome was due to alcoholism and the question of syphilis as an etiological factor left in doubt. The latter supposition is the more probable, experience having shown that in paresis, negative findings throughout are not brought about by the amount of treatment the patient has had.

With faulty diagnoses like the above on the negative side of syphilis, those on the positive side merit citation, for not infrequently patients with obscure pains, febrile attacks, gastric and rectal crises, irritability, failure of memory, etc., give a history of having long been treated for neuresthenia, rheumatism, neuritis, and various other indefinite conditions. Such patients sometimes admit having had a specific infection with indifferent treatment; others disclaim all such knowledge.

One of my clinic patients, a young woman, aged twenty-four years, had within the past two years about twenty attacks of gastric crises. She was usually removed to a hospital, and on two occasions was operated upon, once for appendicitis and again for gall-stones. She has been married five years and has had several miscarriages. The only objective manifestation of tabes was slightly sluggish pupils. Her serum was strongly positive, her spinal fluid showed 45 cells, + + globulin, Wassermann + + + + to 0.6; colloidal gold, luetic curve.

Rectal crises are less commonly seen and their nature often fails of recognition. A patient under my care was treated nineteen years ago for primary and secondary syphilis. For the past two years he had had attacks of severe pain in the rectum, for which an operation had been advised. His pupils were unequal and sluggish to light, knee-jerks normal, station good, bladder slow, sexual power weak. Blood, + + + +; spinal fluid; cells, 150; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, luetic curve. His pains were markedly aggravated by the first few intraspinal treatments.

The so-called lightning pains in tabetics are often treated symptomatically or disregarded entirely.

A patient, aged thirty-four years, infected ten years ago, had suffered from pains in his legs for seven years. His spinal fluid showed: cells, 42; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

Another patient, aged thirty-nine years, infected seven years ago, complained chiefly of stabbing pains in various parts of the body which began four years ago in the lower extremities. His pupils were irregular and sluggish to light, his knee-jerks weak, ankle-jerks absent. Spinal fluid: cells, 8; globulin, + +; Wassermann, + + + + to 0.2; colloidal gold test, luetic curve; serum + + + +.

The premonitory symptoms of developing paresis are also frequently overlooked. This is illustrated by the following case:

Man, aged forty-two years, infection in 1905, for which he was treated for seven years with mercury internally and by injection. He had had no symptoms since 1912. In June, 1915, he had a convulsion, unconsciousness lasting one-half hour. The attack was attributed to colitis and intestinal absorption and treatment directed against this until December, 1915, when he had a second convulsion. His spinal fluid showed: cells, 45; globulin, + + +; Wassermann, + + + + to 0.1; colloidal gold test, paretic curve; serum, + + + +.

In the light of more recent investigations an analysis of the spinal fluid is not complete unless the gold sol test is performed in addition to the Wassermann reaction and cytological and chemical examination. The theory of this reaction is based upon the observation made by Zsigmondy in his original work on metallic colloidal solutions in 1901, that solutions of electrolytes precipitate colloidal gold; that in the absence of an electrolyte, proteins will also cause such a precipitation, while in the presence of an electrolyte they inhibit precipitation. These principles were applied by Lange[2] in 1912 to the examination of the spinal fluid. He found that by a modification of the Zsigmondy technic, normal and pathological fluids could be differentiated from each other as well as syphilitic from other affections of the central nervous system. While the test has been employed by a number of workers during the past few years in the diagnosis of syphilis, it has not had the general application it deserves owing to the difficulty of making the solution. This phase happily is now in large measure overcome by the admirable work of Dr. Miller[3] and his associates. Through their investigations every detail in connection with the technic of its preparation has been so carefully developed that the standardization of the reagent is now possible, and consequently more uniform results in the reaction.

Just how the reaction occurs and the nature of the protein or proteins involved is not known. Views advanced are that it is due to the presence of abnormal albumin or possibly the presence of an excessive amount of the normal. It was originally found that the colloidal gold was a qualitative determination which, according to dilution, gave different reactions. Lange, therefore, sought the explanation in a different qualitative mixture of proteins while Zalozicki interpreted it as an immunity reaction, and Jaeger and Goldstein as a physical phenomenon of an electrical nature. Miller, Brush, Hammers, and Felton have shown that the substance is dialyzable. The amount of albumin normally present in the spinal fluid gives no reaction and a change in reaction is therefore indicative of some abnormality as to quantity or quality.

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[2] Ztschr. f. Chemotherapie, Orig., i, 1912, p. 44.

[3] Bull. Johns Hopkins Hosp., xxvi, 1915, p. 391.

The test itself, very easily and quickly made, consists of a series of color changes which occur so characteristically and constantly that they may be said to be specific. It is performed with ten dilutions of spinal fluid in geometrical progression from 1 to 10 to 1 to 5120. The color change depends on the amount of colloidal gold precipitated and varies from the negative salmon red through red blue, lilac or blue, blue gray or gray, and colorless. These changes may be plotted in curves or are arbitrarily expressed from zero to five. A negative colloidal gold would show no change and would therefore be expressed as 0000000000. In tabes and cerebrospinal syphilis the reaction occurs in the lower dilutions with the intensity of the change in the third and fourth or fourth and fifth tubes. The term "luetic zone" or "luetic curve" is used to describe this reaction. The reading would be as follows: 1133200000 or 1223320000. In meningitis of non-syphilitic origin the maximum change occurs beyond the syphilitic zone—that is, in the higher dilutions—while in paresis precipitation of the colloidal gold occurs regularly in the first four to eight tubes with decolorization or a turbidity, and the reading represented as 5555431000 or as many fives as there are decolorized tubes. To this zonal change Miller and Levy applied the term "paretic curve." A properly standardized—that is, a neutral solution of colloidal gold—shows either no change at all with a normal spinal fluid or produces a slight variation with a bluish nuance in the first four or five tubes which is negligible. Some cases may even give a change to a frank red blue in the first four tubes, so that the reading would be 1111000000, but with all the other laboratory findings negative it has been shown this had no diagnostic import.

It may be said that, as a rule, there is a parallelism between the other positive findings in the fluid and a positive gold reaction. The significance of any one of the individual abnormalities must be appreciated before a proper interpretation can be placed upon the laboratory findings. We know that a lymphocytosis alone is not pathognomonic of syphilis as a mild grade is met with in other affections of the central nervous system and that the cell count cannot be relied upon to differentiate between tabes, cerebrospinal syphilis, and general paresis, as an equally high pleocytosis may be met with in any of these conditions. So too the presence of globulin alone indicates organic disease of the brain or cord, but does not separate syphilitic from non-syphilitic disease. More positive information is derived from the complement-fixation test, as a positive Wassermann occurs only in lues. However, this test by itself does not supply a differential diagnosis as fixation to 0.2 c.c. or lower is met with not only in paresis but in some cases of progressive tabes and cerebrospinal syphilis. On the other hand, with a distinctly syphilitic process, as in cerebral endarteritis, abortive or stationary forms of tabes, and some types of cerebrospinal syphilis, the Wassermann may be completely negative. In the last-named cases a supplementary gold test is of value in demonstrating the luetic nature of the condition. Its greatest value and by far most prominent rôle, however, is in distinguishing between paresis and the conditions which simulate it as well as its prognostic significance in tabetics who show no mental impairment but give a paretic curve. Since the application of the gold sol test in my laboratory a number of patients in whom no cerebral involvement was suspected have given the curve characteristic of paresis. The following cases may be cited as illustrations:

Mr. X., aged thirty-nine years; infection thirteen years ago; secondaries denied. Mercury internally for one and a half years. In 1914 he developed pain in the legs, arms, and neck. When seen by me in March, 1915, his pupils were fixed to light and accommodation; knee-jerks and Achilles-jerks were absent: Romberg was present; slight bladder incontinence; sexual power weak. Spinal fluid examination: cells, 75; globulin, + +; Wassermann, + + + + to 0.4; colloidal gold, decolorization in first five tubes (5555543200). His family had observed no mental trouble, although they thought he had been more irritable and less dependable in business transactions during the preceding year. He has been under active intraspinal treatment; the curve and Wassermann remain unchanged; clinically there has been no change in his condition.

Mr. Y., aged thirty-nine years; infection in 1897. In 1906 had double vision and bladder weakness. In 1912 had tingling in feet, unsteadiness in gait, and great fatigue. He has absent knee-jerks and a Charcot joint of the right hip. The latter part of 1914, according to his family, he was depressed and very forgetful. A spinal-fluid examination made after he had had intensive intravenous and mercurial treatment showed: cells, 2; globulin, + +; Wassermann, + + + + to 0.6. A gold sol test made in May, 1915, read 5555432200.

Mr. Z., aged twenty-seven years. Chancre eight years ago followed by secondaries of the skin and mouth. Treatment internally until 1910, when he developed paralysis of the left external rectus. December 20, 1912, station and gait normal; knee- and ankle-jerks hyperactive; coördination perfect; no sensory changes; objectively viscera normal; pupils normal. Complains of shooting pains in legs, tingling and cramps in calves. Blood Wassermann ——.

Spinal-fluid examination in December, 1913: cells, 26; globulin, +; Wassermann, + + + + to 0.4. Colloidal gold test made in May, 1915, and all subsequent ones give a paretic curve. This patient has had, since the latter part of 1913, 30 intravenous injections of salvarsan and 30 intraspinal injections in addition to mercury. His present fluid examination shows: cells, 3; globulin, + + +; Wassermann, + + + + to 0.4. He is of powerful physique, and during the time he has been under treatment has interrupted his work, which is that of a stationary engineer, only for intraspinal therapy. No change in character or personality has been noted.

In analyzing those cases of general paresis which I have had under my care from time to time the striking feature has been the multiform clinical picture, and in many the absence of the chief symptoms of the affection, namely, the typical cerebral disorders, as writing and speech defects, tremor and memory defects. Some of the patients have had simply a convulsion or two or fainting attacks, while a few others have exhibited no signs referable to the condition, the diagnosis being based mainly on the persistent positive Wassermann reaction and the gold sol test. While it would be premature to make a definite pronouncement as to the prognostic significance of the paretic curve, we must bear in mind the teaching of postmortem findings that anatomical changes in general paresis may long antedate the clinical manifestation. In patients, therefore, who are under continuous observation, and especially those who are receiving intraspinal treatment when the fluid can be examined at regular intervals, the presence or the development of the paretic curve should excite a strong suspicion that these patients may later develop the clinical syndrome. My procedure with these patients is to advise the family or business associates of the possibilities in the case, especially when large business interests are involved, and to treat these cases intensively with the hope that we may anticipate perhaps, retard or arrest, the degenerative cerebral changes. In the type where the meningovascular changes are preponderant, as evidenced by a high cell count, the prognosis is more favorable than where the parenchyma is chiefly involved.

The colloidal gold test has been uniformly positive in all cases with the clinical earmarks of general paresis. In several cases under intensive treatment the paretic curve has changed to the luetic curve. In early syphilis of the central nervous system, *i. e.*, in the early secondary period, I have in several instances found the luetic curve with a negative Wassermann, the only other abnormalities being a slight increase in globulin and lymphocytes. Clinically, these cases gave objective evidence of implication of the central nervous system.

In estimating the number of individuals with abnormal spinal fluids in the secondary stage of the infection I have frequently expressed the conviction that no larger percentage showed definite changes than later developed frank symptoms referable to the neural axis. Further experience strengthens this conviction. In a series of cases examined two years ago abnormalities were demonstrated in less than 20 per cent. In a series of 63 cases recently punctured 10 showed very slight changes as to lymphocytosis and globulin content, coming well within the border-line cases, while 15 exhibited a definite increase in cells and globulin with a positive Wassermann in 7. The cases were all within the first year of infection, untreated or practically so. The standard used was a cell count over 5, a globulin content demonstrated by the Pandy test, a positive Wassermann with 2 c.c. or less of fluid and the color changes elicited by the Lange test. Statistics in the literature treating of abnormal fluids in the secondary stage of lues are variously quoted at from 10 per cent. to 90 per cent. In attempting to reconcile such an apparent disparity it is possible that too much significance has been attached to minor changes, as increased pressure, increase of a few cells, or a trace of globulin. These are probably only transient conditions and part of the systemic infection. My belief is that only such individuals who show very conspicuous changes, as evidenced by a definite cell count, globulin, and positive Wassermann, are candidates for one or the other of the different clinical types of cerebrospinal syphilis. Whether we invoke special conditions as a particular strain or individual predisposition as necessary corollaries to infection of the central nervous system the deduction is forced upon us that in a large majority of patients the organisms must be destroyed spontaneously or by therapeutic agents administered in the ordinary way. The proportion of syphilitics who develop disease of the nervous system is given at from 9 per cent. to 25 per cent. These figures it must be borne in mind were compiled before the era of laboratory diagnoses and their accuracy cannot pass unchallenged.

TREATMENT. In discussing the treatment of syphilis there are certain general considerations in regard to the therapeutic armamentarium worthy of mention. The object of any energetic antiluetic treatment is the destruction of the greatest number of spirochetes in the shortest possible time. From our knowledge of the immunological and pathological processes in the disease this is best accomplished in the early stage, and from experience accrued during the past five years is more readily and more certainly brought about by the combination of salvarsan and mercury. It has been amply demonstrated that salvarsan is essentially a spirocheticide which, while it has very little influence on the organisms in the test tube, is actively germicidal *in vivo*. Mercury is the best-known germicide *in vitro*. When employed experimentally in animals infected with trypanosomiasis or relapsing fever it is practically inert as far as its effect upon the organisms is concerned and the fatal termination of these diseases is not delayed. In spite of this negative evidence, however, it has been demonstrated empirically for many years that mercury has a curative effect in syphilis, and since the cure depends upon the more or less complete saturation of the patient with the drug its action is presumably a direct one. Nor has it been shown that the iodides are spirochetotropic in their action. Potassium iodide has no effect on the early lesions of syphilis and only a neglible one in rendering the Wassermann reaction negative. It has, however, a profound physiological effect aside from its specific therapeutic action. The latter, in gummata, has been explained by Jobling[4] as due to the neutralization of the antiferments which prevent autolysis and absorption of the necrotic tissue, at the same time rendering the infecting organisms which had previously been protected by the necrotic tissue accessible to the parasiticide.

Salvarsan, by virtue of its spirocheticidal properties, finds its greatest field of usefulness in primary and secondary syphilis when the organisms are abundant. In the later stages, when they are few in number and the tissue changes are more marked, one would naturally expect less results from this agent. As a matter of fact, in gummatous and periosteal lesions and all the active manifestations of late syphilis the therapeutic effect of the drug is almost as intense as in the early contagious period. This is especially true of patients who have been treated over a long period of years with mercury and potassium iodide and have become more or less immunized to the action of these drugs. I have seen patients with periosteal lesions and febrile attacks and numerous cases of so-called malignant syphilis in whom mercury and potassium iodide were practically inert very quickly respond to salvarsan. The following case is a typical example:

Woman, aged forty-two years; infection eleven years ago. Treatment for three years by mouth and injections. When seen September 7, 1915, she was suffering from periostitis of the right parietal and frontal bones, of the sternum and right shoulder. For several months she had been running an evening temperature of 101° to 101.5° F., with headache. During this time mercury and potassium iodide were administered without effect. On September 9, 1915, she was given 0.25 gm. salvarsan. Her pains, headache, and fever disappeared in two days, and there was a most marked general improvement. Since that time she has had six small doses of salvarsan and two of neosalvarsan, and has gained over thirty pounds in weight.

While it is possible, theoretically, to formulate a method of treatment in the various stages of syphilis, as a matter of practice the best devised plan must preëminently be an elastic one, subject to the modifications called for by the susceptibility of the patient to the drugs and to intercurrent reactions which take place from time to time.

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[4] Arch. Int. Med., xv, 1915, p. 286.

In early active syphilis, salvarsan alone has been followed by neurorecurrences and monorecurrences or early tertiary lesions. In cases of initial lesion seen before the Wassermann reaction is positive salvarsan may perhaps be given without such danger. It is better, however, not to rely on this drug alone to establish a complete cure but to give the combined treatment. It has been claimed by Wechselman that such combination was more apt to produce kidney involvement, but this contention has not been substantiated by the majority of observers. My own plan is to give a course of mercury with the salvarsan, the number and size of doses of both agents depending upon sex, body weight, and general condition of the patient.

The salvarsan is given in courses of five or six injections in doses of 0.3 gm. to 0.5 gm. for men and 0.25 to 0.4 gm. for women at intervals of one week to ten days. The mercurial injections are given every day or every alternate day if a soluble salt is employed, or once a week if an insoluble one. My preference in case of the former is the bichloride of mercury in courses of twenty to thirty injections given daily or every other day. Of the insoluble preparations, gray oil, (in the form of mercurial cream), of which 5 minims represent one grain, in series of ten to twelve injections, or salicylate of mercury (40 per cent. suspension) in dosage of 1 to 3 grains gradually increased, ten to twelve injections constituting a course. Both salvarsan and mercurial courses are followed by a rest period of six weeks and then the procedure is repeated. Wassermann tests are made periodically, but treatment is not interrupted because of a negative reaction until the adequate amount of medication has been given.

When visceral lesions are present salvarsan should be used in small doses repeated at intervals determined by each case. In cardiac conditions it is better to precede with mercury or mercury and potassium iodide. They are greatly benefited by the latter drug. I have given salvarsan in these cases without untoward symptoms. Whatever form of treatment is decided upon it is important to carry it out persistently. The progress of any active condition can be checked, but anatomical changes like sclerosis or aneurysm are of course permanent.

In primary syphilis before the Wassermann has become positive it is possible to abort the infection both clinically and serologically. While in the past this has been accomplished in some cases with a minimum amount of treatment, such patients now receive two courses each of salvarsan and mercurial injections.

In secondary syphilis with a positive Wassermann it is frequently necessary to give three courses of salvarsan with mercury before the desired effect on the serum reaction is obtained.

In tertiary syphilis the method of treatment depends upon the tissues or organs involved. It is of advantage to combine the courses of salvarsan with intramuscular injections of mercury and to follow this with the prolonged use of potassium iodide and mercury in the form of mixed treatment.

In so-called latent syphilis the administration of salvarsan alone often fails. I have a number of cases in whom the Wassermann reaction continued to show complete inhibition after repeated courses. In many individuals with a positive serum when the nervous system is not involved, careful examination may reveal an aortitis, interstitial glossitis, or the remains of a hepatitis or other viscereal lesion with residua sufficient to call forth a Wassermann reaction. It often requires the most painstaking care to reveal the possible location of the disease. For instance, the nervous system may be implicated and only manifested by slight pupillary irregularity or a slight change in the knee-jerks which might easily be overlooked unless the examination is made by a carefully trained clinician. The spinal fluid should be examined when these deviations are indicative of involvement of the cerebrospinal system, and in all cases with a persistent blood reaction when a focus cannot be determined in the skin, mucous membranes, or viscera. Even in the absence of signs pointing to such implication a Wassermann which does not respond to therapy is an indication for lumbar puncture. More benefit is derived in latent lues from the old-fashioned mixed treatment—that is, a combination of mercury and potassium iodide in a liquid menstruum—than from salvarsan alone or combined simply with potassium iodide. With mixed treatment I have in many instances accomplished the reversal of the Wassermann which had remained persistently positive under salvarsan and mercury.

From Stühmer's[5] experiments the greater part of salvarsan introduced intravenously is stored in the lungs, liver, and spleen in about equal quantities. These form depots from which the drug reaches the circulation, most of it probably passing unchanged through the kidneys and intestines. From the latter a sufficiently large amount is excreted, so that if intestinal disturbance is present marked toxic oxidation products are produced which, when absorbed, may lead to severe reactions.

The reaction following the use of salvarsan may be divided into immediate and delayed.

1. *Immediate.* The commonest symptoms are flushing of the face, cyanosis, a sense of fulness in the head, and precordial distress with slight dyspnea. They usually come on during the administration and may be regarded as anaphylactoid in character. They last but a few minutes and many patients complain of feeling weak or enervated for the next day or two. More rarely patients are met with in whom vomiting occurs during the administration. In a case under treatment this takes place after 15 or 20 c.c. of the solution are introduced. When the attack has passed off the remainder of the

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[5] Arch. f. Derm. u. Syph., cxx, 1914, p. 589.

dose is taken without trouble. A psychical element is probably present in this case. Occasionally attacks of severe pain in the lumbar region come on during the flow of the drug and necessitate its interruption. After half an hour or so it passes off, the patient experiences no further inconvenience, or he may after an hour or more have a chill with temperature and vomiting. These reactions usually come on after several injections have been given.

2. *Delayed.* The symptoms appear after twenty-four hours, three days, or longer. Those after twenty-four hours are usually gastro-intestinal, preceded by a chill or chilly sensation, and are characterized by vomiting and diarrhea with a temperature. In another type there is simply malaise for a few days and then the patients become actively ill with vomiting, fever, and a rash or jaundice, the latter the result in all probability of the action of the arsenic on the liver cells. Rarely suppression of the urine is encountered, and this may be attributable to the direct action of the drug on the renal vessels.

As the majority of the reactions come on only after several doses have been given, one should be warned by their occurrence and regulate the interval and dosage accordingly. In cases in which a dermatitis has been present the drug should not be repeated within six months or a year. I have seen death follow in a patient in whom the significance of such a rash was disregarded during intensive treatment with neosalvarsan. The injections were continued and a most extensive exfoliative dermatitis developed, ending fatally. In my own experience there have been two deaths which may be said to have been directly attributable to salvarsan. In the first, a man, aged forty-two years, the infection was nine years old. For this he had had treatment at intervals for six years. When seen he presented a tubercular ulcerating syphilide of the face, scalp, and left arm. He was given mixed treatment, under which the eruption disappeared. On December 30, 1914, he received 0.35 gm. salvarsan, January 11, 1915, 0.4 gm., January 22, 0.4 gm. After the last treatment he had a slight reaction and a change was made to neosalvarsan, 0.6 gm., on February 10, 1915, which was repeated February 20, 1915. Three days later he developed a temperature of 102° to 104° F., and a generalized dermatitis which partially subsided after a week and then recurred with increased intensity. It involved the entire cutaneous surface, the integument became thickened, leathery-like in consistency, and pigmented. After a few days abscesses developed in various parts of the skin followed by a recurrence in temperature and rapid heart action. These abscesses were opened and drained, but in spite of all the care which could be given the patient death ensued. In this case death could be primarily ascribed to the salvarsan dermatitis and secondarily to the sepsis which followed the cutaneous involvement. The urine showed on March 13 a marked trace of albumin with a few blood and pus cells and a few epithelial casts. On the twenty-third only a trace with a few hyalin casts. It should be added that the patient was markedly alcoholic.

In the second case a woman at the City Hospital, treated in 1911 for an early malignant infection, after the second dose developed suppression of the urine, marked reduction of the blood pressure, vomiting and collapse within twenty-four hours after administration. Autopsy made by Dr. Larkin revealed degenerative changes in the kidney epithelium, in the suprarenal bodies and fatty degeneration of the liver cells.

As mercury has a great affinity for the renal cells the kidney is one of the prime organs to suffer in mercurial intoxication. Hence it is important in the administration of the drug to determine the renal eliminating function and to examine the urine from time to time. From their studies of the various preparations of mercury Schamberg, Kolmer, and Raiziss[6] concluded that the toxicity of the different salts is proportional to the amount of pure mercury contained. After absorption the drug circulates about as a compound of mercury albuminate and sodium chloride, excretion taking place chiefly in the feces and only to a small extent in the urine. It is believed that a definite ratio is maintained between the amount excreted by the kidneys and that present in the general circulation and passing through the renal vessels. The rapidity with which it appears in the urine is taken as an indication of the rapidity and intensity of its effects in the body, its elimination corresponding with its cessation of activity. Its excretion continues for months, and it may appear again after the urine has become free, from which it is deduced that mercury is stored up in the different organs and unless elimination keeps pace with absorption poisoning will result.[7]

When inunctions are employed mercury appears in the urine from the first day on. Elimination gradually increases to a certain point, then remains for weeks nearly constant, and after cessation of treatment falls again gradually.[8] The method is very efficacious, but, unless in the hands of a professional rubber, uncertain. Its disadvantages are constant supervision and filthiness.

When given orally the amount of mercury in the urine shows marked variations from day to day, due apparently to varying conditions affecting absorption from the intestine. With suddenly increased absorption there is danger of mercurialism.[9]

The results of the treatment of syphilis by intramuscular injections of mercurial salts are more rapid after the use of a soluble than an insoluble preparation. The soluble salt is more rapidly efficacious because it is possible to more quickly mercurialize the patient owing to the more rapid absorption and less local reaction. Excretion begins at once, and if given each day elimination rises gradually and regularly, the amount gradually decreasing when stopped. Unfortunately, to be efficient, the injections should be given daily in doses of $\frac{1}{10}$ to $\frac{1}{5}$ grain. This, of course, can be done in hospital wards where patients are under continuous observation, but in dispensary practice and private work it is found to be impracticable because of the frequent visits necessitated. For this reason the insoluble salts have come into use. They form a depot of absorption and require to be administered only at weekly intervals. The rate of absorption is of course much slower, the local reaction more intense and the therapeutic effect slower and less reliable. From animal experiments Schamberg, Kolmer, and Raiziss found that at the end of six or seven weeks almost 50 per cent. of the mercury of insoluble preparations may be unabsorbed at the site of injection. Cases have been reported in which patients weeks or months after treatment suffered from mercurial poisoning when sudden absorption from several foci took place. The elimination curve does not indicate a gradual regular saturation, but maximal elimination occurs on the day of injection and sinks immediately, rising with each new injection. We are now treating all of our cases at the City Hospital with soluble preparations, and we find that some of the most refractory rashes, like the early follicular syphilide, disappear in from two to three weeks even when salvarsan is not given. They are also especially valuable in cerebrospinal syphilis when a rapid effect is desired.

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[6] Jour. Cutan. Dis., xxxiii, 1915, p. 819.

[7] Meyer and Gottlieb, Pharmacology; Clinical and Experimental.

[8] Ibid.

[9] Ibid.

CONCLUSIONS. The fate of the syphilitic individual depends upon the early diagnosis of his infection and the intensity with which treatment is carried out in the first six months. In the accomplishment of this purpose the modern aids to diagnosis have rendered great service. The dark-field illumination furnishes a valuable means of corroboration in all suspicious genital sores and assists in determining the nature of extragenital lesions which may simulate chancre. It should be employed in every case of chancroid to confirm or rule out the possible coincident infection with the Treponema pallidum.

The Wassermann test fills a large field of usefulness not only as a diagnostic medium but as a guide to the effect of treatment and criterion of cure. It is of special value in all conditions of obscure etiology referable to the cardiovascular system, cerebrospinal system, or viscera in which syphilis might be a factor, and in cases with an indefinite clinical picture, such as neuresthenia, febrile attacks, rheumatic pains, etc. Its interpretation is of great importance and requires as much training and experience on the part of the practitioner as does the interpretation of the physical signs.

The examination of the spinal fluid enables us to determine the activity of the luetic process in the brain or cord, to distinguish the various pathological types affecting the central nervous system, and in many cases to differentiate between these and non-syphilitic affections. Recent investigations have shown that an analysis of the spinal fluid is not complete unless the Lange or colloidal gold test is performed in addition to the Wassermann reaction and a cytological and chemical examination. Its chief usefulness lies in distinguishing true paresis from types of cerebrospinal syphilis which simulate it and in diagnosing incipient cases before the clinical syndrome is established. This affects chiefly the prognosis, as our main hope lies in the early diagnosis and treatment of these cases, for when degenerative stigmata are already present the outlook is not so encouraging, for sooner or later relapses occur.

In primary syphilis where the spirochetes are demonstrated and the Wassermann reaction is negative it is possible to cure syphilis with salvarsan alone. It cannot be determined how many doses are required, and as there may be a dissemination of spirochetes even in the presence of a negative Wassermann reaction it is better, therefore, to err on the side of safety and to give at least eight to ten doses and follow this with mercury for perhaps six months.

In secondary syphilis when the early rash is present and the Wassermann positive it is better to precede the salvarsan with several injections of a mercurial salt, preferably a soluble one, on account of the economy of time. In this way an effect is produced on the spirochetes, and when salvarsan is given the temperature reaction and an intensification of the rash—that is, a Herxheimer reaction—can be avoided. After the salvarsan is begun the treatment is to be continued in the manner outlined in the body of the article. The dermatologist and syphilologist should keep in mind the possibility of the involvement of the nervous system in secondary syphilis,.and a complete status should be made when the patient comes under observation so that this record can be compared with any subsequent developments. In this way we are often enabled to detect the very earliest changes which manifest themselves objectively in the nervous system. The most frequent are irregularity of the pupils, persistent headache, and optic neuritis, or auditory disturbance.

In latent syphilis with a positive Wassermann reaction an investigation should be made of the cardiovascular and of the nervous systems or of previous involvement of any of the viscera, as, for instance, syphilitic hepatitis. In cardiovascular syphilis the prolonged use of mercury in connection with potassium iodide is probably of more value than the haphazard use of occasional doses of salvarsan. In other words, in tertiary syphilis with a persistent positive Wassermann reaction without involvement of the central nervous system the beneficial effects of potassium iodide cannot be too strongly insisted upon. In bone and periosteal lesions attended by severe pain there is no drug in the Pharmacopœia that produces so rapid an effect in relieving the pain and reducing the neoplasm.

The criteria of cure are a negative Wassermann reaction for at least a year continuing so after a provocative injection of salvarsan and a normal spinal fluid, with the exceptions which have been noted.

TABLE I.—RESULTS OF TREATMENT IN CASES OF EARLY INFECTION.

Case.	Duration of infection.	Treatment.							Serological result.	Clinical or serological relapse.	Provocative salvarsan.
		Begun.	Ended.	Amount and kind.							
				Salvarsan injections.	Mercury.			Mixed.			
					Injections.	Rubs.	Oral.				
J. M.	2 months	July 15, 1910	July 25, 1911	1	19	35	3 months	...	June 9, 1911 —	None	June 24, 1914 —
G. S.	9 weeks	Feb. 2, 1911	Oct. 1, 1913	2	..	60	3½ months	...	Dec. 6, 1911 —	"	Dec. 17, 1913 —
C. E.	2 months	Feb. 11, 1910	Sept. 15, 1912	2	One and a half years			...	April 26, 1911 —	"	June 17, 1914 —
W. C.	2 months	Nov. 17, 1910	Dec. 22, 1910	3	..	..	..	...	Feb 4, 1911 —	"	Dec. 23, 1914 —
H. N.	2 weeks	Nov. 20, 1911	July 9, 1912	4	17	..	..	...	Oct. 6, 1912 —	"	Mar. 28, 1914 —
B. S.	10 weeks	Nov. 24, 1913	Dec. 10, 1914	17	47	..	..	...	Sept. 14, 1914 —	"	Dec. 6, 1915 —
A. N.	7 months	Sept. 27, 1913	Sept. 9, 1914	17	41	..	..	...	Oct. 9, 1914 —	"	Dec. 28, 1915 —
J. G.	6 weeks	Feb. 19, 1908	Oct. 21, 1910	..	31	..	1 year	1 month	Jan. 25, 1911 —	"	Feb. 20, 1915 —
S. W.	6 weeks	Dec. 30, 1910	July 27, 1911	2	13	10	..	...	June 11, 1913 —	"	
R. Y.	3½ months	Jan. 14, 1911	July 9, 1912	7	..	..	..	...	Mar. 11, 1911 —	"	
G. B.	5 weeks	April 10, 1911	Jan. 15, 1912	3	..	9 weeks	2 months	...	May 4, 1912 —	"	
T. C.	1 month	Oct. 21, 1912	Nov. 9, 1912	4	..	..	..	...	Always —	"	
H. C.	4 weeks	Jan. 23, 1914	Oct. 30, 1914	10	21	..	..	...	April 18, 1914 —	"	
G. C.	5 weeks	July 31, 1914	April 14, 1915	10	24	..	..	...	Nov. 18, 1914 —	"	
C. A.	6 weeks	Dec. 15, 1913	Oct. 17, 1914	6	25	..	..	...	Always —	"	
J. C.	2 months	June 13, 1914	Mar. 2, 1915	9	25	..	..	...	Sept. 17, 1914 —	"	
H. N.	4 months	Nov. 10, 1913	May 29, 1914	13	13	..	..	...	May 27, 1914 —	"	
R. G.	8 weeks	Aug. 16, 1913	June 2, 1914	12	19	..	..	...	June 13, 1914 —	"	
W. C.	6 weeks	Aug. 15, 1905	Oct. 6, 1909	..	50	..	7 months	6 months	Oct. 24, 1913 —	"	

TABLE II.—RESULTS FOLLOWING PROVOCATIVE INJECTION.

Case.	Date of Infection.	Wassermann before treatment.	Treatment.						Wassermann.	Clinical or serological relapse.	Provocative salvarsan.
			Begun.	Ended.	Amount and kind.						
					Salvarsan injection.	Mercury.					
						Injection.	Rubs.	Oral.			
P. A.	1880	4+	Dec. 2, 1909	June 18, 1912	1	61	...	...	Dec. 6, 1913 –	None	Jan. 14, 1914 ++++
J. B.	1897	(?)	1897	1900	..	...	...	2½ years	Oct. 30, 1912 –	"	Nov. 12, 1912 ++++
C. M.	1910	(?)	Oct. 10, 1914	Feb. 1, 1915	..	50	...	...	April 3, 1915 –	Has tabes	April 14, 1915 ++++
J. A.	1901	(?)	1901	1905	..	1½ years	3 years	...	Mar. 15, 1916 ±	Gummata	Mar. 23, 1916 ++++
E. K.	Hereditary, 7 years old	±	No treatment Parents syphilitic	No symptoms	..	..	...	...	....	....	Provoc. KI Oct. 7, 1915 Wassermann Mar. 1, 1916 ++++
J. C.	1890	(?)	1890	1899	..	..	8 years	6 months	1909 –	None	Jan. 23, 1912 –
W. H. S.	June, 1913	4+	Dec. 2, 1913	Oct. 1, 1914	10	44	...	...	Nov. 24, 1914 –	"	Sept. 12, 1915 –
T. P.	(?) third stage	4+	Sept. 20, 1913	April 11, 1914	16	42	...	...	May 11, 1914 –	"	Oct. 20, 1915 –
J. E. H.	Feb. 2, 1914	4+	April 14, 1914	Dec. 1, 1914	16	38	...	...	Jan. 25, 1915 –	"	Nov. 27, 1915 –
S. D.	(?) third stage	4+	Sept. 24, 1913	Sept. 15, 1914	17	49	...	...	Oct. 16, 1914 –	"	Feb. 9, 1916 –
G. E. G.	(?) third stage	4+	May 19, 1914	July 9, 1915	13	50	...	...	July 9, 1915 –	"	Dec. 20, 1915 –
M. R.	May, 1914	4+	July 8, 1914	June 15, 1915	15	46	...	...	Feb. 3, 1916 –	"	Dec. 19, 1915 –
B. S.	Miscarriages	4+	Dec. 26, 1913	Feb. 30, 1915	10	47	...	...	Mar. 2, 1915 –	"	Feb. 7, 1916 –
B. S.	Sept., 1913	4+	Nov. 24, 1913	Dec. 1, 1914	17	47	...	...	Sept. 14, 1914 –	"	Dec. 6, 1915 –
C. B.	April, 1914	4+	Dec. 29, 1914	Dec. 15, 1915	15	45	...	...	July 22, 1916 –	"	Feb. 8, 1916 –
A. N.	Jan., 1913	4+	Sept. 27, 1913	Sept. 9, 1914	17	51	...	...	Oct. 9, 1914 –	"	Jan. 24, 1916 –
A. Mc.	May, 1914	4+	July 12, 1914	July 15, 1915	17	42	...	...	Feb. 15, 1916 –	"	Jan. 3, 1916 –
T. M.	1908	4+	Oct. 21, 1912	July 7, 1913	9	22	...	...	Sept. 11, 1913 –	"	Dec. 27, 1915 –

TABLE III.—INTRACTABLE REACTIONS AFTER PERSISTENT TREATMENT.

Case.	Date of infection.	Wassermann before treatment.	Treatment.					Wassermann after treatment.	Clinical relapses during treatment.	Remarks.
			Amount and kind.				Duration.			
			Salvarsan injections.	Mercury.		Mixed.				
				Injections.	Rubs.					
W. Z.	Nov., 1911	++++	14	45	...	....	1½ years	++	None	Clinically negative.
B. H.	April 26, 1913	++++	16	36	...	....	1 year	+	"	Clinically negative.
F. G.	April, 1912	++++	20	26	...	....	1½ years	±	"	Clinically negative.
A. R.	1909	++++	22	36	4 months	4 months	2 years	++++	"	Clinically negative; spinal fluid negative.
W. W.	1899	++++	10	31	...	8 months	2½ years	++++	"	Has remains of hepatitis.
L. H.	Dec., 1912	++++	15	101	4 months	18 weeks	2¾ years	++	"	Has aortitis.
I. D.	Mar., 1913	++++	12	72	...	6 months	2½ years	+	"	Has aortitis.
J. B.	Denied	++++	17	10	...	6 months	1½ years	++++	"	Large aneurysm present.
R. H.	1907	++++	23	30	88	16 weeks	2 years	++++	"	Optic atrophy; spinal fluid positive.
F. M.	1903	++++	9	32	...	....	7 months	++++	"	Tabes; spinal fluid positive.
G. M.	1902	++++	20	60	6 months	1 year	2½ years	++++ ++++	"	Spinal fluid positive; cerebrospinal syphilis.
E. R.	1904	++++	31	40	...	....	1½ years	++++	"	Has paresis; spinal fluid positive.
M. D.	Congenital 20 years ago	++++	18	36	...	2 years	3 years	++++ ++++	"	Remains of keratitis; deafness; spinal fluid negative.